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FAMILIAL AND SECOND PRIMARY PANCREATIC CANCERS: A NATIONWIDE EPIDEMIOLOGIC STUDY FROM SWEDEN

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Familial risk of pancreatic cancer has been mainly assessed through case-control studies based on reported but not medically verified cancers in family members. We used the nationwide Swedish Family-Cancer Database on 10.2 million individuals and 21,000 pancreatic cancers to calculate standardized incidence ratios (SIRs) and 95% confidence intervals (CIs) for pancreatic cancer in 0- to 66-year-old offspring of parents with pancreatic or other specified tumors. Additionally, SIRs for second primary pancreatic cancers were analyzed after any first neoplasm. SIRs for pancreatic cancer (1.68, 95% CI 1.16–2.35) and pancreatic adenocarcinoma (1.73, 95% CI 1.13–2.54) were increased when a parent presented with pancreatic cancer. The risk was not dependent on diagnostic age of offspring or parents. Pancreatic cancer was associated with parental lung, rectal or endometrial cancer and with melanoma. SIRs for pancreatic cancer were 10.01 and 7.96 among offspring who were diagnosed before age 50 years when parents were diagnosed with squamous cell and adenocarcinoma of the lung, respectively, before age 60 years. The population-attributable proportion of familial pancreatic cancer was 1.1%. Risks for second pancreatic cancers were increased in men and women after small intestinal, colon and bladder cancer. The degree of familial clustering for pancreatic cancer and its population-attributable proportion were lower than the data cited in the literature. Clustering of pancreatic cancer with sites presenting in hereditary nonpolyposis colorectal cancer was noted. The strong association of pancreatic and lung cancers is puzzling, and it remains unclear to what extent this represents familial sharing of smoking habits.

Key words: *pancreatic cancer; familial cancer; Sweden*

Cancer of the exocrine pancreas is a ductal adenocarcinoma in 85–90% of cases.[1] Worldwide incidence ranges between 1 and 10 cases/100,000 as the world standard rate; rates in developed countries are in the upper part of this range, *e.g.,* 5/100,000 for Swedish women and marginally higher for men.[2] Known or suspected risk factors for pancreatic cancer include tobacco smoking, chronic pancreatitis, diabetes, diet poor in fruit and vegetables and rich in calories and meat, and family history.[1,3–5] Pancreatic cancer is a manifestation in a number of cancer syndromes, *e.g.,* hereditary nonpolyposis colorectal cancer (HNPCC), *BRCA2* mutation, *p16*-linked melanoma-pancreatic cancer, familial pancreatitis and Peutz-Jeghers syndrome, the gene defects of which are known.[1,6–8] Pancreatic cancer clusters also in families, though the genes involved have not been identified.[9–11] However, there is a large difference between estimates of familial risk for pancreatic cancer and the proportion of familial cases. The range in the reported familial risk spans from the nonsignificant (1.25) to the highly significant (18)[12–16] and in the proportion of familial cases (3–16%).[1,15,17] One problem may be that most earlier studies relied on reported, rather than medically confirmed cancers in family members, which may entail considerable false reporting in any cancer because the familial cases may have occurred decades apart.[13,18–21] Even in the U.S. National Familial Pancreas Tumor Registry, only the diagnosis of index patients is confirmed. For intraabdominal cancers and particularly for pancreatic cancer, a special problem may be the distinction from primary liver cancer.[13,18–21] Challenging the data from case-control studies, the Utah population database gave the lowest familial risk of 1.25, with data originating from a cancer registry.[12]

Because of the limited population-based data on familial clustering of pancreatic cancer, we examined here familial risks and the occurrence of pancreatic cancer as a second primary malignancy using the nationwide Swedish Family-Cancer Database.[22] Multiple primary cancers may be informative of the same environmental and genetic factors that influence first primaries, in addition to the treatment-related effects.[23] Pancreatic cancer patients have a poor survival, and it is not meaningful to follow second cancers during this short survival period; instead, we report data on second primary pancreatic cancers following first primary cancers of at least moderate survival.[24] The Database was updated in 2000 to include over 10 million individuals and over 1 million registered tumors. It offers unique possibilities for reliable estimation of familial risks because the data on family relationships and cancers were obtained from registered sources of practically complete coverage.

MATERIAL AND METHODS

The Swedish Family-Cancer Database was created in the mid-1990s by linking an administrative family register on all Swedish families to the Swedish Cancer Registry.[22,25] For each child, there are data on both parents at the time of birth. Each person is assigned a unique technical identification number (which is different from the national identification number, or "personal number"), allowing construction of families, *e.g.,* through the mother. The Database includes all persons born in Sweden after 1931 with their biologic parents, totaling over 10.2 million individuals. It was updated in 2000 to include cancers from the nationwide Swedish Cancer Registry from 1958 to 1998. The Database includes 3.2 million families, with parents and offspring.

The completeness of cancer registration in the 1970s has been estimated to be >95% and is now considered to be close to 100%. The percentage of cytologically or histologically verified cases of pancreatic cancer is close to 100% for patients diagnosed before age 50 years and 85% for all ages.[26] This has been 70% or more throughout the history of the Swedish Cancer Registry. In an *ad hoc* study on gastric adenocarcinoma, the completeness of the cancer registry was 98%.[27] The Swedish Family-Cancer Database has a practically complete coverage of all individuals and their cancers. However, a proportion of deceased offspring lack information on 1 or both parents, particularly affecting offspring who were born between 1932 and 1940 or who died before 1991.[22] Of a total of 7 million offspring, 216,000 died by the end of follow-up,

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31 December 1998. Parental information was missing from 15,000 offspring who had a diagnosis of cancer (9.9% of all offspring cancers). This deficit is likely to cause some underestimation of familial risk estimates in the present study because pancreatic cancer has a high mortality. However, because most of the persons with incomplete parental information were born in the 1930s or died before 1991, we were able to estimate the effects by comparing familial risks in different birth cohorts and diagnostic periods.

The Swedish Cancer Registry is based on compulsory notification of cases.[26] A 4-digit diagnostic code according to the ICD-7 was used. The following ICD-7 codes were pooled: upper aerodigestive tract cancer, codes 161 (larynx) and 140–148 (lip, mouth, pharynx), except for code 142 (salivary glands), and leukemia, codes 204–207 (leukemias), 208 (polycythemia vera) and 209 (myelofibrosis). According to the ICD-7 classification, lymphomas, including pancreatic ones, are classified as lymphomas irrespective of the site at which they occur. Codes for histologic classification were used to confirm that close to 90% of specified histologies were adenocarcinomas.

Family history information was collected on all first-degree relatives (parents, siblings and children), but only parent–offspring relationships were used in the present study because of the lack of affected sibling pairs (only 1 affected sibling pair, which is within expected values, *i.e.,* 1254 offspring cases/3.2 million families; thus, 0.5 families would be expected to have 2 cases). All tumor incidence rates were based on the data in the Swedish Family-Cancer Database. Age standardization was according to the world standard population. The risk of pancreatic cancer was calculated for offspring whose parents presented with pancreatic cancer or any other specified tumor and compared to the rate of pancreatic cancers among all offspring. Results were tabulated if at least 2 familial pairs were found. Follow-up was started at birth or 1 January 1961, whichever came latest. Follow-up was terminated on cancer diagnosis, death, emigration or the closing date of the study, 31 December 1998. Standardized incidence ratios (SIRs) were calculated as the ratio of observed to expected numbers of cases. Expected numbers were calculated from 5-year age-, sex-, tumor type-, region-, period- and socioeconomic status-specific standard incidence rates. Confidence intervals (95% CIs) were calculated assuming a Poisson distribution. SIRs for second cancers were calculated in a similar way, starting follow-up from the diagnosis of the first tumor. All individuals, parents and offspring were included in the analysis of second events. To be included, the first malignancies had to have a median survival of at least 2 years,[24] which was not met by esophageal, gastric, liver, pancreatic and lung cancers. At least 5 cases had to be observed for men or women. Even synchronous second cancers were included, and the follow-up time was divided into 3 periods, allowing assessment of the effect of follow-up time. The population-attributable proportion of cases with a family history of pancreatic cancer was estimated as follows: proportion of familial cases $\times$ (familial SIR – 1)/familial SIR.[28]

RESULTS

The Swedish Family-Cancer Database covered years 1961–1998 from the Swedish Cancer Registry and included 1,254 offspring aged 0–66 years and 19,929 parents with pancreatic cancer (Table I). A total of 34 offspring (familial proportion 2.71%) had a parent affected with pancreatic cancer, and they had accumulated 1.5 million person-years at risk; these were calculated for offspring of affected parents throughout the follow-up time, irrespective of the time of parental diagnosis. The whole offspring generation in the Database accumulated a total of 168 million person-years. The median age at diagnosis was 54 years for offspring and 68 years for parents. Average family size was 2.2 and 2.3 for families with 2 cases and all families, respectively.

We assumed that socioeconomic and regional factors could be confounding factors for familial risk. Table II shows the relative risks of pancreatic cancer by these variables. Relatively small differences were noted: self-employed men and professional men and women had the highest incidence and farmers the lowest. Residence in large cities carried a small risk for men only. These variables were adjusted for in the analysis of familial risk. Incidence trends for pancreatic cancer in the Database are shown in Figure 1 for the period 1961–1998. Initially, the rate for women was only 60% of that for men, but the incidence for women increased by the end of the 1980s almost to the level for men.

TABLE I – CHARACTERISTICS OF THE STUDY POPULATION

Pancreatic cancer cases	
Offspring	1,254
Person-years in offspring	168.2 million
Familial cases	34
Person-years (when affected parent)	1.5 million
Parents	19,929
Median age at diagnosis (years)	
Offspring	54
Parents	68
Average family size	
Families with 2 cases	2.2
Any family	2.3

Familial risks for offspring pancreatic cancer were calculated by type of parental cancer (Table III). The data in this and subsequent tables were adjusted for age, period, residential area and socioeconomic status, all of which may influence the incidence of pancreatic cancer. Only cancer sites associated with at least 2 offspring pancreatic cancers were listed in Table III. The SIR for pancreatic cancer in offspring was 1.68 (95% CI 1.16–2.35) when a parent presented with pancreatic cancer. However, this was entirely due to male offspring, whose SIR was 2.17 (95% CI 1.38–3.26) but independent of the male or female proband. The SIR for offspring pancreatic cancer was 1.73 (95% CI 1.13–2.54) for pancreatic adenocarcinoma. Pancreatic cancer was also associated with parental lung cancer (SIR = 1.52) and, among sons, from parental rectal (SIR = 1.60) and endometrial (SIR = 1.89) cancer. To control for the possible effects of missing parental data, analysis was carried out separately for offspring born before 1940 or later and only including families with complete parental data. SIRs for offspring pancreatic cancer were 1.69, 1.67 and 1.61, respectively, suggesting that the small proportion of offspring, particularly those born in the 1930s, with lacking links to parents did not influence the results. The SIR was 1.64 for pancreatic cancer diagnosed after 1990, when the highest proportion of offspring was linked to parents. Using the familial proportion of 2.71% from Table I and the SIR of 1.68 from Table III, the population-attributable proportion of familial pancreatic cancer is 1.1%.

Limiting offspring to those diagnosed before 50 years of age decreased the SIR for pancreatic cancer from a parental proband concordant cancer to a nonsignificant 1.45 (Table IV). However, the association with parental lung cancer increased to 2.16, and with parental melanoma the SIR was 2.58. Limiting parental age to 60 years increased the SIR by concordant pancreatic cancer to 2.44 (95% CI 0.88–5.35); by parental lung cancer, the risk was 3.14. When the offspring age was limited to 50 years and that of parents to 60 years, parental lung cancer was associated with offspring pancreatic cancer (SIR = 4.40), which was the only association to reach statistical significance. Pancreatic cancer was associated particularly with parental squamous cell carcinoma (SIR = 10.01) and adenocarcinoma (SIR = 7.96) of the lung, whereas no increase was observed with other histologic types (large and small cell carcinoma).

SIRs for second primary pancreatic cancers following all male (father and son) cancers are shown in Table V for first cancer with at least 2 years of survival. The SIR from all sites was increased to 1.85 during the first year of follow-up, to 1.25 during 1–10 years and to 1.61 later. The SIR for pancreatic cancer was over 10 after small intestinal and breast cancer during the first year. Pancreatic cancer was even increased after colon and renal cancers through all

TABLE II – AGE-STANDARDIZED RELATIVE RISK OF PANCREATIC CANCER BY SOCIOECONOMIC STATUS AND REGION

	Men			Women		
	Number of cases	Relative risk	95% CI	Number of cases	Relative risk	95% CI
Socioeconomic status						
Agriculture	1,560	0.91	0.86–0.96	1,147	0.94	0.89–1.00
Self-employed	982	1.09	1.02–1.16	699	0.99	0.92–1.07
Professional	393	1.09	0.98–1.20	272	1.06	0.94–1.19
Blue collar	2,544	0.98	0.94–1.02	2,458	0.98	0.94–1.02
Worker	4,604	1.01	0.97–1.04	3,322	1.03	0.99–1.07
Others	893	1.04	0.97–1.11	890	1.01	0.94–1.08
Region						
Large cities	3,810	1.08	1.04–1.12	2,943	1.03	0.98–1.07
Southern parts	2,712	1.02	0.98–1.06	2,161	1.02	0.97–1.07
Northern parts	4,454	0.93	0.90–0.97	3,684	0.97	0.93–1.01
All[1]	10,976	1.00	0.97–1.03	8,788	1.00	0.97–1.03

[1]Reference.

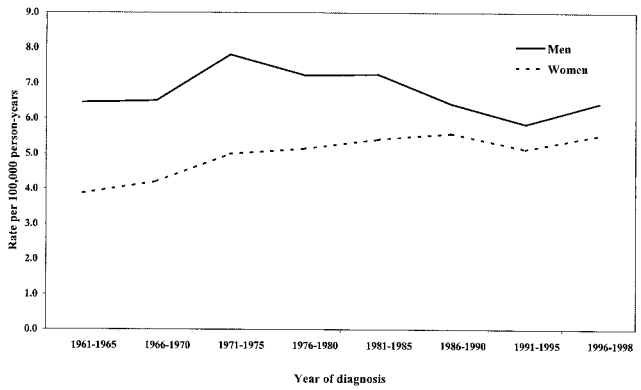

FIGURE 1 – Age-standardized incidence of pancreatic cancer (adjusted to world standard population) in the Swedish Family-Cancer Database for 1961–1998.

follow-up periods. Bladder and particularly testicular cancers were linked to an excess of pancreatic cancer toward the end of follow-up. Even cancer of the upper aerodigestive tract and prostate, Hodgkin's disease and leukemia were associated with an excess of pancreatic cancer among all subjects.

Similar patterns of increase for second pancreatic cancer were observed for women than for men, though the overall risk of 1.30 was somewhat lower among women (Table VI). In the initial period, increases after small intestinal, colon and bladder cancers were observed. After breast, cervical and ovarian cancers and melanoma, the increase in pancreatic cancer took place toward the end of follow-up.

DISCUSSION

The Swedish Family-Cancer Database contains national family data linked to the Swedish Cancer Registry. The incidence of pancreatic cancer in the database is identical to Swedish Cancer Registry data up to age 65 years, whereas at higher age the rates deviate somewhat due to differences in population structure.[22] The inability to link some 10% of deceased offspring diagnosed with cancer to their parents may potentially cause underestimation of familial risk of fatal cancers, such as pancreatic cancer. However, as the missing links predominantly influence those born in the 1930s and those who died before 1991 and as we saw no difference in familial risks in comparing these offspring groups, we conclude that the gap in parental links has no large effect on the present estimates. The large number of comparisons is another technical point worth consideration. Undoubtedly, some associations were due to chance, and consistency within this study and between studies as well as biologic plausibility should be assessed for causal inference.

The present study provides evidence on familial risks in pancreatic cancer in the 0- to 66-year-old population. The risk to offspring was significant, 1.68 from concordant parental cancer and 1.73 from pancreatic adenocarcinoma, consistent with adenocarcinoma being the predominant histologic type. Because 2.71% of parents were affected by pancreatic cancer, the population-attributable risk of all pancreatic cancers was 1.1%. A recent authoritative treatise on digestive tract tumors states that 3–10% of pancreatic cancer cases are familial, giving a higher figure than our 2.71%.[1] However, even case-control studies cite familial risks of 5–18%[15,16] which are higher than other case-control results[4,14] and appear to conform to the pattern that case-control studies tend to overestimate the degree of familial clustering of cancer. To what extent environmental factors contribute to familial clustering remains unknown. However, 2 clues suggest that they do, perhaps to an appreciable extent. Firstly, pancreatic cancer is one of the few cancer types that show spousal concordance; *i.e.,* pancreatic cancer in 1 spouse is a risk factor for the second spouse, which is only partially attributable to smoking.[29] Secondly, the data in Table IV show that the observed familial risk is not clearly age-dependent, failing to follow the pattern of conventional hereditary cancers. However, the offspring population was still young, below 67 years; thus, the median diagnostic age for pancreatic cancer in offspring was 54 years, 14 years below that in parents, weakening any conclusions about the possible age dependence.

Pancreatic cancer is a manifestation in a number of cancer syndromes, of which HNPCC is the most common.[1,30] In the present analysis, we found some evidence for the involvement of HNPCC, particularly associated with rectal and endometrial cancers. Among other syndromes, *BRCA2* mutations may explain the high risk of pancreatic cancer after male breast cancer (Table V), and evidence on *p16*-linked melanoma-pancreatic cancer clustering was noted among offspring diagnosed before age 50 years (Table IV). However, an interesting novel association was revealed between pancreatic and lung cancers. Although tobacco smoking is likely to contribute to this association, it is probably not its main cause. Smoking is a much weaker risk factor for pancreatic (2- to 3-fold risk) than for lung (20-fold risk) cancer, and the 2 generations do not fully match in their smoking habits.[1,30] Furthermore, this association was strongest for squamous cell carcinoma and adenocarcinoma, and it showed a clear age dependence, the risk being 4.40 for offspring diagnosed before age 50 years when parents were diagnosed before age 60 years. In this group, the risk from parental squamous cell carcinoma was as high as 10.01 and that for adenocarcinoma was 7.96. Although the frequency of male smoking is less in Sweden than in any other European Union country, the possible contribution of smoking to a rare disease remains likely.[31] Smoking shows a social class dependence, and some effect of smoking was most likely con-

TABLE III – SIR FOR PANCREATIC CANCER IN OFFSPRING BY CANCER IN PARENTS

Parental cancer	Son			Daughter			All offspring		
	Observed	SIR	95% CI	Observed	SIR	95% CI	Observed	SIR	95% CI
Upper aerodigestive tract	11	1.53	0.76–2.75	9	1.35	0.61–2.57	20	1.44	0.88–2.23
Esophagus	1	0.38	0.00–2.18	1	0.43	0.00–2.48	2	0.40	0.04–1.49
Stomach	24	1.29	0.82–1.92	12	0.70	0.36–1.23	36	1.01	0.71–1.40
Small intestine	2	1.49	0.14–5.50	0			2	0.79	0.07–2.91
Colon	24	0.99	0.64–1.48	18	0.83	0.49–1.31	42	0.91	0.66–1.24
Rectum	22	**1.60**	**1.00–2.42**	13	1.06	0.56–1.82	35	1.34	0.94–1.87
Anus	2	4.19	0.40–15.42	0	0.00	2.32–9.48	2	2.25	0.21–8.26
Liver	14	1.28	0.70–2.15	14	1.43	0.78–2.41	28	1.35	0.90–1.95
Pancreas	23	**2.17**	**1.38–3.26**	11	1.14	0.56–2.04	34	**1.68**	**1.16–2.35**
Adenocarcinoma	15	**1.85**	**1.03–3.06**	11	1.59	0.79–2.86	26	**1.73**	**1.13–2.54**
Lung	29	1.34	0.89–1.92	33	**1.73**	**1.19–2.43**	62	**1.52**	**1.17–1.95**
Breast	31	0.96	0.65–1.37	29	1.02	0.68–1.46	60	0.99	0.75–1.27
Cervix	6	0.93	0.33–2.04	7	1.18	0.47–2.44	13	1.05	0.56–1.80
Endometrium	15	**1.89**	**1.05–3.12**	6	0.84	0.30–1.84	21	1.39	0.86–2.13
Ovary	6	0.80	0.29–1.74	3	0.45	0.08–1.33	9	0.63	0.29–1.21
Prostate	51	1.18	0.88–1.55	36	0.93	0.65–1.29	87	1.06	0.85–1.31
Other male genital	0			2	4.03	0.38–14.81	2	2.01	0.19–7.38
Kidney	14	1.31	0.71–2.20	7	0.74	0.29–1.53	21	1.04	0.64–1.59
Urinary bladder	16	1.11	0.63–1.81	13	1.01	0.54–1.73	29	1.06	0.71–1.53
Melanoma	9	1.62	0.73–3.08	8	1.63	0.70–3.23	17	1.62	0.94–2.60
Skin	7	0.67	0.26–1.38	7	0.72	0.29–1.49	14	0.69	0.38–1.17
Eye	1	1.15	0.00–6.58	1	1.26	0.00–7.25	2	1.20	0.11–4.43
Nervous system	8	1.01	0.43–2.00	6	0.86	0.31–1.89	14	0.94	0.51–1.59
Thyroid gland	4	1.80	0.47–4.67	3	1.46	0.28–4.33	7	1.64	0.65–3.40
Endocrine glands	3	0.64	0.12–1.90	5	1.22	0.39–2.87	8	0.91	0.39–1.81
Connective tissue	4	2.14	0.56–5.54	1	0.59	0.00–3.37	5	1.40	0.44–3.29
Non Hodgkin's lymphoma	9	1.11	0.50–2.12	6	0.83	0.30–1.81	15	0.98	0.55–1.62
Hodgkin's disease	2	1.39	0.13–5.12	1	0.74	0.00–4.24	3	1.08	0.20–3.18
Myeloma	5	0.99	0.31–2.33	4	0.85	0.22–2.21	9	0.92	0.42–1.76
Leukemia	8	0.91	0.39–1.80	5	0.62	0.20–1.47	13	0.77	0.41–1.33
All	351	**1.20**	**1.08–1.34**	261	1.00	0.88–1.13	612	**1.11**	**1.02–1.20**

Bold type, 95% CI does not include 1.00. Sites were included if 2 or more cases were observed.

TABLE IV – SIR FOR PANCREATIC CANCER IN OFFSPRING BY CANCER IN PARENTS

Parental cancer	Offspring <50 years			Parent <60 years			Offspring <50 years, parent <60 years		
	Observed	SIR	95% CI	Observed	SIR	95% CI	Observed	SIR	95% CI
Colon	16	1.37	0.78–2.24	8	1.46	0.62–2.89	3	1.35	0.25–4.00
Rectum	12	1.80	0.93–3.16	5	1.45	0.46–3.40	1	0.73	0.00–4.19
Pancreas	7	1.45	0.57–3.00	6	2.44	0.88–5.35	2	2.03	0.19–7.47
Lung	25	**2.16**	**1.40–3.19**	18	**3.14**	**1.86–4.97**	11	**4.40**	**2.19–7.91**
Adenocarcinoma	7	**3.00**	**1.19–6.21**	3	3.95	0.75–11.70	3	**7.96**	**1.50–23.57**
Squamous cell carcinoma	11	**3.02**	**1.50–5.42**	6	**4.01**	**1.44–8.78**	6	**10.01**	**3.60–21.93**
Others	5	1.54	0.49–3.62	7	**3.70**	**1.47–7.67**	1	1.41	0.00–8.07
Breast	22	1.16	0.73–1.76	16	0.99	0.56–1.61	7	0.96	0.38–1.99
Endometrium	7	1.49	0.59–3.08	9	1.97	0.89–3.76	3	1.69	0.32–5.00
Prostate	28	1.35	0.90–1.95	1	0.37	0.00–2.15	1	0.91	0.00–5.24
Urinary bladder	12	1.62	0.83–2.84	5	1.57	0.49–3.68	2	1.47	0.14–5.42
Melanoma	10	**2.58**	**1.23–4.76**	5	1.92	0.61–4.52	4	2.81	0.73–7.27
All	188	**1.26**	**1.08–1.45**	111	**1.21**	**1.00–1.46**	42	1.10	0.79–1.48

Bold type, 95% CI does not include 1.00.

trolled by the adjustment for socioeconomic status and region. In a previous study, spousal correlation was observed also between pancreatic and lung cancers.[29,32]

There was an overall excess of second primary pancreatic cancers following any cancer. Practically all tumor notifications registered at the Swedish Cancer Registry bear a histologic or cytologic verification, excluding false reporting as the cause for the increase in second cancers.[33] However, any treatment-related effects would be expected to manifest only about a decade after diagnosis of the first cancer.[34,35] Studies on patients with Hodgkin's disease, a relatively early-onset malignancy, who received radio- and chemotherapy have shown contradictory results for pancreatic cancer; however, they suggest that pancreatic cancer is uncommonly a result of treatment.[34,35] In the present study, Hodgkin's disease was followed by an excess of pancreatic cancer in men, and the effect of treatment could not be excluded. A significant increase in pancreatic cancer in the late follow-up period was noted after testicular cancer (Table V). Two anticancer agents, cisplatin and etoposide, were used in the treatment of testicular cancer in the 1970s and 1980s, respectively. However, our data showed no evidence that the risk of second pancreatic cancer was related to these drugs because the increase was not limited to the end of the follow-up period.

Small intestinal and colon cancers caused an increase in second pancreatic cancers in men and women. The likely explanation is that these cancers presented synchronously with pancreatic cancer or that pancreatic cancer was diagnosed during the treatment, causing a lead-time bias. A large excess of second pancreatic cancer has also been observed after carcinoid

TABLE V – SIR FOR SECOND PANCREATIC CANCER IN MEN

First primary cancer	Follow-up interval (years)											
	<1			1–10			>10			All		
	Observed	SIR	95% CI	Observed	SIR	95% CI	Observed	SIR	95% CI	Observed	SIR	95% CI
Upper aerodigestive tract	3	1.34	0.25–3.96	35	**1.61**	**1.12–2.23**	12	1.21	0.62–2.12	50	**1.47**	**1.09–1.94**
Salivary gland	1	6.67	0.00–38.22	4	2.84	0.74–7.34	1	1.14	0.00–6.51	6	2.46	0.89–5.39
Small intestine	8	**24.24**	**10.35–48.00**	4	2.47	0.64–6.38	1	1.72	0.00–9.88	13	**5.14**	**2.72–8.81**
Colon	14	**2.56**	**1.40–4.31**	51	**1.55**	**1.16–2.04**	21	**2.05**	**1.27–3.14**	86	**1.77**	**1.42–2.19**
Rectum	8	2.18	0.93–4.32	13	0.55	0.29–0.94	11	1.63	0.81–2.93	32	0.94	0.64–1.32
Breast	2	**18.18**	**1.71–66.87**	2	2.02	0.19–7.43	0			4	2.82	0.73–7.28
Prostate	30	1.36	0.92–1.95	182	1.15	0.99–1.33	16	0.89	0.51–1.44	228	**1.15**	**1.01–1.31**
Testis	0			3	1.74	0.33–5.16	14	**4.88**	**2.66–8.21**	17	**3.62**	**2.11–5.82**
Kidney	9	**3.61**	**1.64–6.89**	24	**1.70**	**1.09–2.53**	12	**2.22**	**1.14–3.89**	45	**2.04**	**1.49–2.74**
Urinary bladder	8	1.50	0.64–2.98	68	**1.46**	**1.13–1.85**	29	**1.95**	**1.31–2.80**	105	**1.57**	**1.28–1.90**
Melanoma	0			11	0.70	0.35–1.26	5	0.73	0.23–1.71	16	0.67	0.38–1.08
Skin	5	1.56	0.49–3.68	30	1.07	0.72–1.53	8	1.21	0.52–2.40	43	1.14	0.82–1.53
Eye	0			4	2.13	0.55–5.50	3	3.23	0.61–9.55	7	2.35	0.93–4.87
Nervous system	3	2.10	0.40–6.21	4	0.65	0.17–1.67	4	0.98	0.26–2.54	11	0.94	0.47–1.69
Thyroid gland	1	3.70	0.00–21.23	4	1.80	0.47–4.66	3	2.04	0.38–6.04	8	2.02	0.86–4.00
Endocrine glands	0			7	1.11	0.44–2.31	8	2.19	0.93–4.33	15	1.43	0.80–2.36
Connective tissue	1	2.38	0.00–13.65	6	1.99	0.72–4.37	2	1.37	0.13–5.04	9	1.84	0.83–3.51
Non-Hodgkin's lymphoma	3	1.42	0.27–4.21	14	1.19	0.65–2.00	4	1.54	0.40–3.98	21	1.27	0.79–1.95
Hodgkin's disease	0			4	2.48	0.65–6.42	4	3.60	0.94–9.32	8	**2.67**	**1.14–5.28**
Myeloma	3	2.48	0.47–7.34	7	1.24	0.49–2.56	1	2.00	0.00–11.46	11	1.49	0.74–2.68
Leukemia	3	1.42	0.27–4.19	17	1.54	0.89–2.46	4	2.07	0.54–5.36	24	**1.59**	**1.02–2.37**
All	102	**1.85**	**1.51–2.24**	494	**1.25**	**1.14–1.36**	163	**1.61**	**1.37–1.88**	759	**1.37**	**1.28–1.48**

Bold type, 95% CI does not include 1.00.

TABLE VI – SIR FOR SECOND PANCREATIC CANCER IN WOMEN

First primary cancer	Follow-up interval (years)											
	<1			1–10			>10			All		
	Observed	SIR	95% CI	Observed	SIR	95% CI	Observed	SIR	95% CI	Observed	SIR	95% CI
Upper aerodigestive tract	0			3	0.67	0.13–1.97	2	0.99	0.09–3.64	5	0.71	0.22–1.67
Salivary gland	1	10.00	0.00–57.32	0			1	0.88	0.00–5.07	2	0.79	0.07–2.90
Small intestine	6	**30.00**	**10.80–65.73**	2	1.61	0.15–5.93	1	2.04	0.00–11.70	9	**4.66**	**2.11–8.89**
Colon	16	**3.95**	**2.25–6.43**	31	1.08	0.73–1.53	13	1.08	0.57–1.85	60	**1.34**	**1.02–1.72**
Rectum	3	1.62	0.31–4.80	12	0.85	0.43–1.48	9	1.50	0.68–2.86	24	1.09	0.70–1.62
Breast	10	0.99	0.47–1.82	135	1.12	0.94–1.32	92	**1.41**	**1.14–1.73**	237	**1.21**	**1.06–1.37**
Cervix	1	1.05	0.00–6.03	21	**1.72**	**1.06–2.63**	35	**1.54**	**1.07–2.14**	57	**1.59**	**1.20–2.05**
Endometrium	2	0.84	0.08–3.08	33	1.08	0.75–1.52	35	1.35	0.94–1.88	70	1.19	0.93–1.51
Ovary	5	2.45	0.77–5.77	24	**1.67**	**1.07–2.49**	19	**1.72**	**1.03–2.69**	48	**1.75**	**1.29–2.32**
Other female genitals	0			5	1.38	0.44–3.25	4	2.22	0.58–5.75	9	1.54	0.70–2.93
Kidney	0	0.00	0.72–2.95	13	1.48	0.78–2.53	8	1.79	0.76–3.54	21	1.44	0.89–2.20
Urinary bladder	5	**4.35**	**1.37–10.23**	18	**1.71**	**1.01–2.71**	9	1.93	0.88–3.68	32	**1.96**	**1.34–2.77**
Melanoma	0			11	0.83	0.41–1.49	16	**1.84**	**1.05–2.99**	27	1.17	0.77–1.71
Skin	2	1.36	0.13–5.00	21	1.60	0.99–2.44	3	0.71	0.13–2.10	26	1.38	0.90–2.02
Eye	0			5	**3.85**	**1.21–9.05**	1	1.08	0.00–6.16	6	2.56	0.92–5.62
Nervous system	1	0.84	0.00–4.82	10	1.19	0.57–2.20	9	1.31	0.59–2.50	20	1.22	0.74–1.88
Thyroid gland	1	2.50	0.00–14.33	5	1.05	0.33–2.48	7	1.27	0.50–2.63	13	1.22	0.65–2.09
Endocrine glands	1	0.93	0.00–5.31	17	1.15	0.67–1.84	9	1.09	0.50–2.09	27	1.12	0.74–1.63
Connective tissue	0			1	0.51	0.00–2.91	0			1	0.28	0.00–1.61
Non-Hodgkin's lymphoma	3	2.29	0.43–6.78	6	0.74	0.27–1.63	5	2.18	0.69–5.14	14	1.20	0.65–2.02
Hodgkin's disease	0			0			2	2.63	0.25–9.68	2	1.08	0.10–3.95
Myeloma	1	1.37	0.00–7.85	6	1.57	0.57–3.44	1	2.63	0.00–15.08	8	1.62	0.69–3.21
Leukemia	3	2.61	0.49–7.72	4	0.57	0.15–1.47	3	1.86	0.35–5.52	10	1.02	0.49–1.89
All	61	**1.79**	**1.37–2.30**	383	**1.17**	**1.05–1.29**	284	**1.43**	**1.27–1.61**	728	**1.30**	**1.21–1.40**

Bold type, 95% CI does not include 1.00.

tumors, most of which were intestinal, supporting the operation of lead-time bias rather than diagnostic misclassification.[36] The associations between colon and pancreatic cancers may also be due to HNPCC because pancreatic cancer was even increased after other HNPCC-related sites, including the ovary, kidney and bladder.[37,38] As pointed out earlier, the association between male breast cancer and pancreatic cancer may be due to *BRCA2* mutation carriers. Tobacco smoking is a shared factor, which could explain the association between upper aerodigestive tract and pancreatic cancers.

In summary, using the data on medically verified diagnosis and registered family structures, we showed a 1.68-fold increase in pancreatic cancers among 0- to 66-year-old offspring of parents with pancreatic cancer. The population-attributable proportion of familial clustering was 1.1%. The degree of familial clustering is much lower than that found in many earlier case-control studies. There was a strong familial association between lung and pancreatic cancers, reaching an SIR of 10.01 for pancreatic cancer in young offspring when parents presented with squamous cell lung cancer.

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